

CLAIMS:

1. (+)- or (-)-*erythro*-Mefloquine hydrochloride in a crystalline form which exhibits a characteristic X-ray powder diffraction pattern with peaks expressed in d-values (Å) of: 5.95 (s) and 4.02 (w).
- 5 2. Mefloquine hydrochloride according to claim 1, wherein the pattern also has peaks, expressed in d-values (Å), of:
11.2 (vs), 9.0 (s), 7.4 (w), 6.8 (w), 6.3 (s), 6.1 (m), 6.0 (m), 5.95 (s), 5.58 (m),
5.42 (m), 4.91 (m), 4.87 (w), 4.74 (s), 4.55 (w), 4.16 (vs), 4.12 (s), 4.10 (s), 4.02
(w), 3.82 (vs), 3.77 (w), 3.74 (s), 3.71 (vs), 3.64 (m), 3.47 (w), 3.40 (w), 3.33 (w),
10 3.31 (m), 3.27 (w), 3.25 (w), 3.11 (m), 3.04 (m), 2.94 (m), 2.92 (w), 2.75 (w), 2.70
(m), 2.68 (w), 2.64 (m), 2.62 (m), 2.54 (w), 2.45 (w), 2.39 (w), 2.35 (w), 2.30 (w),
2.29 (w), 2.25 (w), 2.22 (w), 2.18 (w), 2.17 (w), 2.08 (w), 1.99 (m), 1.95 (w), 1.91
(w), and 1.88 (w).
- 15 3. (+)- or (-)-*erythro*-Mefloquine hydrochloride comprising particles having a
size distribution of 30 to 150 µm, in a crystalline form which exhibits a X-ray
powder diffraction pattern with peaks expressed in d-values (Å) of:
22.3 (vw), 11.2 (vs), 9.0 (w), 8.2 (vw), 7.4 (vw), 6.8 (vw), 6.5 (vw), 6.3 (vw), 6.1
(vw), 6.0 (vw), 5.94 (vw), 5.61 (m), 5.42 (w), 4.89 (vw), 4.74 (w), 4.54 (w), 4.12
(s), 4.02 (w), 3.81 (vvs), 3.74 (vs), 3.70 (vw), 3.64 (vw), 3.55 (w), 3.47 (vw), 3.40
20 (vw), 3.34 (vw), 3.31 (vw), 3.26 (vs), 3.11 (vw), 3.04 (w), 2.97 (vw), 2.94 (vw),
2.81 (vw), 2.75 (m), 2.71 (w), 2.69 (w), 2.64 (w), 2.62 (w), 2.54 (vw), 2.46 (vw),
2.43 (vw), 2.40 (vw), 2.35 (vw), 2.30 (vw), 2.27 (vw), 2.24 (vw), 2.22 (vw), 2.17
(vs), 2.08 (vw), 2.06 (vw), 2.04 (vw), 1.94 (w), 1.91 (vw) and 1.88 (vw).
- 25 4. (+)- or (-)-*erythro*-Mefloquine hydrochloride comprising particles having a
size distribution of 1 to 10 µm, in a crystalline form which exhibits a characteristic
X-ray powder diffraction pattern with peaks expressed in d-values (Å) of:
11.2 (m), 9.0 (w), 8.30 (vw), 7.4 (vw), 6.8 (vw), 6.3 (w), 6.1 (vw), 6.0 (vw),
5.95 (vw), 5.59 (w), 5.42 (w), 4.91 (vw), 4.74 (w), 4.55 (vw), 4.16 (w), 4.12 (s),
4.03 (w), 3.82 (vvs), 3.75 (w), 3.71 (w), 3.64 (w), 3.55 (w), 3.47 (vw), 3.40 (vw),
30 3.33 (w), 3.26 (w), 3.11 (vw), 3.04 (vw), 2.94 (vw), 2.75 (w), 2.71 (vw), 2.69 (vw),
2.64 (w), 2.62 (vw), 2.54 (vw), 2.46 (vw), 2.43 (vw), 2.40 (vw), 2.35 (vw), 2.30
(vw), 2.26 (vw), 2.22 (vw), 2.17 (w), 2.08 (vw), 2.06 (vw), 1.99 (vw), 1.91 (vw) and

1.89 (vw).

5. Mefloquine hydrochloride according to any of claims 1 to 4, which exhibits a characteristic X-ray powder diffraction pattern as exhibited in any of Figures 1, 2 and 3.

5 6. (+)- or (-)-*erythro*-Mefloquine hydrochloride in a crystalline form which exhibits characteristic Raman bands, expressed in wave numbers (cm^{-1}), of: 1030.2 (w) and 85.4 (vs).

7. (+)- or (-)-*erythro*-Mefloquine hydrochloride in a crystalline form which exhibits characteristic Raman bands, expressed in wave numbers (cm^{-1}), of:
10 2877 (m), 1601 (s), 1585 (s), 1363 (vs), 1028.2 (w), 320 (m) and 118 (vs).

8. (+)- or (-)-*erythro*-Mefloquine hydrochloride which, as an acetone solvate, is in the form of a crystalline pseudo-polymorph which exhibits characteristic Raman bands, expressed in wave numbers (cm^{-1}) of :

1602 (s), 1585 (s), 1363 (vs), 322 (m) and 118 (vs).

15 9. (+)- or (-)-*erythro*-Mefloquine hydrochloride which, as a tetrahydrofuran solvate, is in the form of a crystalline pseudo-polymorph which exhibits characteristic Raman bands, expressed in wave numbers (cm^{-1}), of:

1601 (s), 1585 (s), 1363 (vs), 323 (m) and 119 (vs).

10. (+)- or (-)-*erythro*-Mefloquine hydrochloride which, as a methyl ethyl
20 ketone solvate, which exhibits characteristic Raman bands, expressed in wave numbers (cm^{-1}), of:

1600 (s), 1585 (s), 1363 (vs), 319 (m) and 118 (vs).

11. Mefloquine hydrochloride according to any preceding claim, which is substantially in the form of thick columns, cuboids, cubes or cube-like particles.

25 12. (+) or (-)-*erythro*-Mefloquine hydrochloride in crystalline form B or C, which is substantially in the form of thick columns, cuboids, cubes or cube-like particles.

13. A process for the preparation of mefloquine hydrochloride according to any of claims 1 to 6, which comprises dissolution of another solid form of (+)- or
30 (-)-*erythro*-mefloquine hydrochloride at a temperature from 20°C to 100°C in a solvent, to form a concentrated solution, optionally seeding and cooling the solution to precipitate (+)- or (-)-*erythro*-mefloquine hydrochloride, stirring the

suspension for a time sufficient to complete formation of the desired crystalline form, removing the solvent, and drying the solid residue.

14. A process for the preparation of mefloquine hydrochloride according to any of claims 1 to 6, which comprises dissolution of another solid form of (+)- or (-)-*erythro*-mefloquine hydrochloride at a temperature from 20°C to 100°C in a solvent, to form a concentrated solution, optionally seeding and adding a sufficient amount of a non-solvent to precipitate (+)- or (-)-*erythro*-mefloquine hydrochloride, stirring the suspension for a time sufficient to complete formation of the desired crystalline form, removing the solvent, and drying the solid residue.

15. A process for the preparation of a crystalline form of (+)- or (-)-*erythro*-mefloquine hydrochloride, comprising the steps of:

- a) dissolving or suspending substantially water-free (+)- or (-)-*erythro*-mefloquine free base at a temperature from 10 to 80°C in ethanol,
- 15 b) adding aqueous HCl and water at a concentration, such that the formed (+)- or (-)-*erythro*-mefloquine hydrochloride is insoluble,
- c) shaking or stirring the resultant suspension and optionally also cooling it, and
- d) isolating the precipitate and drying the solid residue.

20 16. A process according to claim 15, comprising the steps of:

- a) dissolving or suspending substantially water-free (+)- or (-)-*erythro*-mefloquine free base at a temperature from 40 to 80°C in ethanol,
- b) maintaining the temperature and adding aqueous HCl to form (+)- or (-)-*erythro*-mefloquine hydrochloride under shaking or stirring,
- 25 c) slowly decreasing the temperature continuously or continuously and stepwise down to about 10°C to 30°C,
- d) adding water at the decreased temperature to reduce solubility of (+)- or (-)-*erythro*-mefloquine hydrochloride,
- e) shaking/stirring at the decreased temperature, and
- 30 f) isolating the precipitate and drying the solid residue.

17. A process according to claim 15, for the preparation of mefloquine hydrochloride according to any of claims 1 to 6, in form of cubes or cube-like

forms, comprising the steps of:

- a) dissolving or suspending substantially water-free (+)- or (-)-*erythro*-mefloquine free base at a temperature from 65 to 80°C in absolute ethanol,
 - 5 b) maintaining the temperature and continuously adding within 5 to 20 minutes under shaking or stirring concentrated aqueous HCl such that the water content in the ethanol/water mixture is from 20 to 3 and preferably 15 to 5 volume percent, to form a solution of (+)- or (-)-*erythro*-mefloquine hydrochloride in ethanol/water,
 - 10 c) continuously decreasing the temperature at a rate of 0.2 to 1K/min down to about 20°C to 30°C, or continuously decreasing the temperature in a first step at a rate of 0.2 to 1K/min 5 to 20°C lower as in step a), adding 0.5 to 2.5 percent by weight, referred to the amount of (+)- or (-)-*erythro*-mefloquine hydrochloride, of crystal seeds of the mefloquine hydrochloride according to any of claims 1 to 6, in cubic or cube-like
15 morphological form, stirring for 15 to 30 minutes, and then continuously decreasing the temperature at a rate of 0.1 to 1K/min down to about 20°C to 30°C,
 - d) adding water at the decreased temperature over 30 to 60 minutes in such
20 amount that the water content in the ethanol/water mixture is from 65 to 85 volume percent,
 - e) continuing shaking/stirring for 1 to 2 hours at the decreased temperature, and
 - f) isolating the precipitate and drying the solid residue.
- 25 18. A process for the manufacture of (+)- or (-)-*erythro*-mefloquine hydrochloride according to claim 7, comprising the steps of:
- a) treating with or without vacuum a methyl ethyl ketone solvate of (+)- or (-)-*erythro*-mefloquine hydrochloride at a temperature from 20°C to 100°C, preferably 30°C to 70°C, to remove the methyl ethyl ketone, or
 - 30 b) suspending a methyl ethyl ketone solvate of (+)- or (-)-*erythro*-mefloquine hydrochloride in a non-solvent, stirring for a time sufficient to remove methyl ethyl ketone from the solvate, and isolating and then drying the

crystals.

19. A process for the manufacture of (+)- or (-)-*erythro*-mefloquine hydrochloride according to any of claims 8 to 10, comprising the steps of:

- 5 a) dissolving (+)- or (-)-*erythro*-mefloquine hydrochloride in acetone, tetrahydrofuran or methyl ethyl ketone at a temperature from 40 to 80°C to form a concentrated, saturated or super-saturated solution, cooling and stirring the cooled suspension for a time period sufficient to form the solvate, and isolating and drying the crystals, or
- 10 b) suspending (+)- or (-)-*erythro*-mefloquine hydrochloride in acetone or tetrahydrofuran, stirring the suspension at a temperature from 20 to 35°C for a time sufficient to form the solvate, and isolating and drying the crystals.

20. Mefloquine hydrochloride according to any of claims 1 to 12, for use in therapy.

- 15 21. Use of mefloquine hydrochloride according to any of claims 1 to 12, for the manufacture of a medicament for use in the treatment of malaria, a movement or neurodegenerative disorder, or a inflammatory or autoimmune disease.